Listing of the Claims

This listing of the claims replaces all the prior versions and listings of the claims.

1. (Currently amended) A method of prolonging expression of a heterologous gene encoding a prodrug activating enzyme in a neoplastic cell transduced with a vector encoding the prodrug activating enzyme comprising

a) transducing the neoplastic cell transduced with a vector encoding the prodrug activating enzyme with a vector encoding an apoptosis inhibiting agent, wherein the apoptosis inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFIAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP, ScIAP, Bcl-XL, and Mc1-1, and

wherein expression of the apoptosis inhibiting agent results in prolonged lifespan of the neoplastic cell thereby increasing expression of the prodrug activating enzyme compared to a life span of a cell not transduced with the vector encoding the apoptosis inhibiting agent.

2. (Cancelled)

3. (Currently amended) The method of claim 1 further comprising contacting the transduced neoplastic cell of step a) with a prodrug, wherein the prodrug activating enzyme is selected from the group consisting of cytochrome P450, NADPH-P450 reductase, cytosine deaminase, nitroreductase, thymidine phosphorylase, purine nucleoside phosphorylase, alkaline phosphatase, carboxypeptidase A, carboxypeptidase G2, linamarase, beta-lactamase, xanthine oxidase, guanine phosphoribosyl transferase (GPT), deoxycytidine kinase, uracil phosphoribosyltransferase, carboxylesterase, and folylpolyglutamate synthetase.

4.-7. (Cancelled)

8. (Currently amended) The method of claim 3, wherein the prodrug is selected from the group consisting of cyclophosphamide (CPA) and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase; ~~ganciclovir,~~

~~acyclovir and their analogs~~; 5-fluorocytosine; CB1954 and other aromatic nitro prodrugs; 5'-deoxy-5-fluorouridine; 6-methylpurine-2'-deoxynucleoside; etoposide phosphate; methotrexate-(phenyl)alanine; benzoic acid mustard-glucuronide; amygdalin; cephalosporin-mustard carbamate; xanthine; 6-thioxanthine; cytosine arabinoside; 5-fluorouracil; irinotecan (CPT-11); edatrexate.

9. (Original) The method of claim 3, wherein the prodrug activating enzyme is cytochrome P450 and the prodrug is cyclophosphamide or ifosfamide.

10. (Original) The method of claim 9, wherein the prodrug-activating cytochrome P450 enzyme is selected from the group consisting of CYP 1A1, 1A2, 1B1, 2A6, 2B1, 2B6, 2B11, 2C3, 2C5, 2C6, 2C7, 2C8, 2C9, 2C11, 2C18, 2C19, 3A1, 3A2, 3A3, 3A4, 3A5 and 3A7.

11. (Currently amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target neoplastic cell in a mammal in need thereof comprising the steps of:

a) transducing the target neoplastic cell with a first vector comprising a nucleic acid encoding a prodrug activating enzyme, wherein the prodrug activating enzyme is selected from the group consisting of cytochrome P450, NADPH-P450 reductase, cytosine deaminase, nitroreductase, thymidine phosphorylase, purine nucleoside phosphorylase, alkaline phosphatase, carboxypeptidase A, carboxypeptidase G2, linamarase, beta-lactamase, xanthine oxidase, guanine phosphoribosyl transferase (GPT), deoxycytidine kinase, uracil phosphoribosyltransferase, carboxylesterase, and folylpolyglutamate synthetase;

b) transducing the target neoplastic cell with a second vector comprising a nucleic acid encoding an apoptosis inhibiting agent, wherein the apoptosis inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFIAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP, ScIAP, Bcl-XL, and Mc1-1; and

c) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a)

wherein expression of the nucleic acid encoding an apoptosis inhibiting agent increases the life span of the transduced target neoplastic cell compared to a cell not transduced with an apoptosis inhibiting agent when the mammal is subjected to the prodrug.

12. (Cancelled)

13. (Currently amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target neoplastic cell in a mammal in need thereof comprising the steps of:

a) transducing the target neoplastic cell with a vector comprising a nucleic acid encoding a prodrug activating enzyme wherein the prodrug activating enzyme is selected from the group consisting of cytochrome P450, NADPH-P450 reductase, cytosine deaminase, nitroreductase, thymidine phosphorylase, purine nucleoside phosphorylase, alkaline phosphatase, carboxypeptidase A, carboxypeptidase G2, linamarase, beta-lactamase, xanthine oxidase, guanine phosphoribosyl transferase (GPT), deoxycytidine kinase, uracil phosphoribosyltransferase, carboxylesterase, and folylpolyglutamate synthetase; and a nucleic acid encoding an apoptosis inhibiting agent, wherein the apoptosis inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFIAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP, ScIAP, Bcl-XL, and Mc1-1 and

b) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a)

wherein expression of the nucleic acid encoding an apoptosis inhibiting agent increases the life span of the transduced target neoplastic cell compared to a cell not transduced with an apoptosis inhibiting agent when the mammal is subjected to the prodrug.

14. (Previously presented) The method of claim 11, wherein the apoptosis inhibiting agent is expressed under control of a regulatable promoter.

15. (Previously presented) The method of claim 1, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a factor that promotes apoptosis expressed under control of a regulatable promoter.

16. (Original) The method of claim 15, wherein the factor that promotes apoptosis is selected from the group consisting of Smac/Diablo a caspase, p53, Bax, Bak, Bcl-Xs, Bad, Bik, Bid, apoptosis inducing factor, and anti-sense or siRNA directed against the apoptosis inhibiting agent, an IAP or other anti-apoptotic factor.

17. (Previously presented) The method of claim 11, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a death receptor ligand expressed under control of a regulatable promoter.

18. (Original) The method of claim 17, wherein the death receptor ligand is selected from the group consisting of TNFα, Trail and Fas ligand.

19-30. (Cancelled)

31. (Previously presented) The method of claim 13, wherein the apoptosis inhibiting agent is expressed under control of a regulatable promoter.

32. (Previously presented) The method of claim 13, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent, further comprises a factor that promotes apoptosis expressed under control of a regulatable promoter.

33. (Previously presented) The method of claim 13, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a death receptor ligand expressed under control of a regulatable promoter.

34-36. (Cancelled)

37. (Currently Amended) A method for increasing vector spread in a host comprising administering to the host a vector system, wherein the vector system comprises a replicating vector encoding a prodrug activating enzyme and a non-replicating vector

encoding an apoptosis inhibiting agent, wherein expression of the apoptosis inhibiting agent results in prolonged lifespan of the neoplastic cell thereby increasing expression of the prodrug activating enzyme compared to a life span of a cell not transduced with the vector encoding apoptosis inhibiting agent and a vector encoding the prodrug activating enzyme, wherein the apoptosis inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFIAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP, ScIAP, Bcl-XL, and Mc1-1, and wherein the replicating vector encoding the prodrug activating enzyme is administered prior to, concurrently with or after the administration of the non-replicating vector encoding the apoptosis inhibiting agent.

38. (Currently Amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of a target neoplastic cell in a tumor in a mammal affected with the tumor comprising the steps of:

a) transducing the target neoplastic cell in the tumor with a first vector comprising a nucleic acid encoding a prodrug activating enzyme;

b) transducing the target neoplastic cell in the tumor with a second vector comprising a nucleic acid encoding an apoptosis inhibiting agent; and

c) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a);

wherein expression of the nucleic acid encoding the apoptosis inhibiting agent increases the life span of the transduced target neoplastic cell in the tumor when the mammal is subjected to the chemotherapeutic drug compared to a life span of a neoplastic cell not transduced with a vector comprising a nucleic acid encoding the apoptosis inhibiting agent.